The effects of the angiotensin II receptor (type I) antagonist irbesartan in patients with cardiac syndrome X

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About 20% of patients undergoing cardiac catheterisation with a clinical suspicion of coronary artery disease have normal coronary arteries. Amongst this heterogeneous population, a sub-group has been identified with several features in common; these features have been termed cardiac syndrome X.[1] This syndrome is generally defined as angina-like chest pain occurring in association with a positive exercise tolerance test (ETT) and/or positive myocardial perfusion scan and angiographically normal coronary arteries but in the absence of cardiovascular disease.[2] Despite an excellent prognosis in terms of survival, a significant proportion of these patients continue to experience long-term chest pain which can be disabling or poorly responsive to treatment and often undergo repeated hospital admissions.[3] [4]

The primary aim of treatment is symptomatic control. However, few of the pharmacological trials to date have evaluated the effects of treatment on chest pain or related symptoms as opposed to ECG evidence of ischaemia. The pathophysiology of cardiac syndrome X remains unclear and appears heterogeneous. Common to all patients, however, is anginal-type chest pain and an "ischaemic" response on stress testing in the presence of normal epicardial coronary arteries, suggesting an important role for dynamic small vessel constriction.

Angiotensin II (ATII) is a powerful vasoconstrictor involved in the control of coronary vascular resistance and in facilitating sympathetic nerve influences in the heart. Both of these actions are potentially important in cardiac syndrome X where reduced coronary flow and increased sympathetic drive may be important in the genesis of chest pain. Blocking these ATII effects may thus be beneficial in cardiac syndrome X.

To date, one small trial using the angiotensin-converting enzyme (ACE) inhibitor enalapril has shown a significant reduction in anginal chest pain and ECG evidence of ischaemia on exercise testing.[5] ACE inhibitors, however, only block ATII generation via the classical pathway, but by contrast ATII antagonists completely inhibit angiotensin effects and in addition are selective in blocking ATII effects. Thus, if ATII is important in cardiac syndrome X, such drugs should be at least as effective as ACE inhibitors and possibly more effective due to more complete ATII blockade. To our knowledge, to date no trial of ATII antagonists in cardiac syndrome X has been reported.

METHODS

This was a double-blind, randomised, placebo-controlled, two-period crossover study conducted at the Royal Liverpool University Hospital to assess the tolerability and efficacy of irbesartan on chest pain, exercise tolerance and ECG evidence of myocardial ischaemia during treadmill exercise and during the activities of daily living.

The study protocol was approved by Liverpool Research Ethics Committee. All subjects gave full written informed consent prior to any study procedures.

Patients with a documented diagnosis of cardiac syndrome X, as defined above, were recruited. All cardiovascular drugs were stopped for a 2-week washout phase. Patients were randomised to receive either irbesartan 150 mg daily or matching placebo for 1 week following a positive baseline treadmill ETT. Holter 24 h ECG monitoring measured the number of episodes of ST depression, total ischaemic burden (TIB) and heart rate variability. After 1 week the study medication was increased to 300 mg daily for a further 2 weeks.

After the initial treatment period of 3 weeks, a second ETT was performed 2 h after dosing, followed by Holter ECG monitoring. Following a second 2-week washout phase, the patients crossed over to the other study medication for a further 3 weeks of treatment conducted in identical fashion.

During the study, the patients recorded symptoms, tolerability and overall efficacy. Episodes of chest pain were counted and the severity of each episode was assessed by the patient. Glyceryl trinitrate (GTN) consumption was also noted.

The safety of irbesartan compared to control was observed and evaluated by physical examination at each visit.

Descriptive statistics were used for the demographic variables of age, gender, race and baseline clinical values. Continuous variables were expressed as mean±standard deviation (SD). The change in each variable from baseline and at 3 weeks in both the irbesartan and placebo groups was measured and the difference was then compared and assessed by the two-tailed paired Student's t test.

RESULTS

A total of 43 patients were screened for entry into the study. Twenty eight patients were randomised, and of these 24 completed the study and were eligible for the efficacy analyses.

The subjects were characteristic of the cardiac syndrome X population,[3] with the majority (89%) being women and the mean±SD age being 53.5 ± 9.29 years. Of the 28 patients randomised, 27 were Caucasian (96%) and one was Asian (4%). Baseline clinical characteristics of the patients were similar between the two groups, with a mean heart rate of 81 ± 14 bpm, a mean systolic blood pressure of 135 ± 16 mm Hg and a mean diastolic blood pressure of 77 ± 10 mm Hg.

The patients' chest pain symptoms and GTN consumption after 3 weeks of treatment together with the results of the exercise tolerance testing are shown in table 1.

Exercise duration was significantly increased by placebo. However, during Holter monitoring the total number of episodes of 1 mm ST segment depression (-25 v 5; p = 0.095) and TIB (p = 0.141) showed a non-significant improvement

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Abbreviations: ACE, angiotensin-converting enzyme; ATII, angiotensin II; ETT, exercise tolerance test; GTN, glyceryl trinitrate; SD, standard deviation; TIB, total ischaemic burden

Table 1 Results following 3 weeks of treatment

Variable	Change with irbesartan (ΔI)	Change with placebo (ΔP)	ΔI−ΔP	Statistics
Chest pain episodes				
Total	−58	−25	−33	n = 24
Mean	−2.42	−1.04	−1.38	t = −1.58
SD	3.57	2.71	4.27	p = NS
GTN consumption (puffs)				
Total	−34	−18	−16	n = 24
Mean	−1.42	−0.75	−0.67	t = −0.93
SD	3.71	4.01	3.51	p = NS
ETT				
Total exercise time (s)	−116	686	−802	n = 24
Mean	−4.83	28.6	−33.4	t = 4.90
SD	78.2	85.9	111	p<0.001 for placebo
Time to onset of chest pain (s)	n = 21	n = 18		
Total	1393	805	780	n = 17
Mean	66.3	44.7	45.9	t = 1.04
SD	124	128	181	p = NS
Time to ST depression (s)	(n = 24)	(n = 20)		
Total	275	687	−632	n = 20
Mean	11.5	32.7	−31.6	t = −1.34
SD	71.0	91.0	105	p = NS
TIB at end of test (mm)				
Total	−33	−38.5	5.5	n = 24
Mean	−1.38	−1.60	0.23	t = 0.24
SD	2.46	3.45	4.63	p = NS
Number of leads with ST depression				
Total	−15	−23	8	n = 24
Mean	−0.63	−0.96	0.33	t = 0.55
SD	1.38	2.56	2.95	p = NS

ETT, exercise tolerance test; GTN, glyceryl trinitrate; SD, standard deviation; TIB, total ischaemic burden.

with irbesartan. Neither had a significant effect on heart rate variability.

Irbesartan and placebo were equally well tolerated.

DISCUSSION

The results of our study show that the angiotensin II receptor (type I) antagonist irbesartan produced no significant subjective or objective improvements in patients with cardiac syndrome X. With irbesartan only the reduction in the number of Holter episodes of ST segment depression approached significance (p = 0.095), while placebo significantly increased treadmill exercise time.

Several study limitations should be considered. The study population was small and only a single centre was involved. Recruitment was slow due to the unwillingness of patients to undergo the four ETTs included in the study. This caused a longer than expected total study duration and resulted in the exercise tests being carried out by five different doctors. The study duration was short and possibly not long enough to allow maximum potential effects of the medication.

Therefore, the results of this small study do not support the use of the ATII blocker irbesartan in patients with cardiac syndrome X.

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